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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,902	07/03/2003	Hiroshi Takeyama	Q76104	8672

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EXAMINER	
LEWIS, AMY A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,902	TAKEYAMA ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/27/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Case

The Preliminary Amendment, filed 3 July 2003, has been received and entered into the application. Accordingly, claims 2-17 have been amended. Claims 1-17, as filed on 3 July 2003, are presented for examination.

Priority

Acknowledgement is made of Applicant's claim for foreign priority, under 35 U.S.C. § 119(a)-(d), to Japanese Application No. 2002-34145, filed 25 November 2002; the certified copy was filed in the instant application on 3 July 2003.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-3, 5, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Bessette (WO 00/33857).

Bessette teaches a pharmaceutical composition for the treatment of soft tissue cancer in mammals comprising at least one plant essential oil compound and a specific embodiment where the plant oil is benzyl alcohol (see: abstract; reference claims 1, 2, 8, and 14) – see current

claims 1 and 3. The reference also teaches oral and parenteral administration (p. 6) as well as topical application to the skin (p. 7), which meets the limitation of current claim 2 and 8 as to external administration) of the composition to a patient in need thereof. The reference specifically teaches treatment of human breast cancer cells (MCF-7) with 50 μg/ml benzyl alcohol (see: p. 6; p. 11-12, Example 3) and thus, anticipates current claims 2, 8, and 9 as to breast and other cancers.

2) Claims 1-3, 5, 8, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by "The antitumor effect to stomach cancer by benzyl alcohol," Meeting of Japan Surgical Society on April 12-14, 2000, issued on March 10, 2000, PP-1457 (listed on PTO Form 1449, dated 27 October 2003, with a translation provided by Applicant), hereafter referred to as "Reference PP-1457."

Reference PP-1457 teaches that benzyl alcohol induced cell death by apoptosis in stomach cancer cells (in the cell line STKM) thereby anticipating current claims 1, 3, 5, and 9.

In reference to the limitation in instant claims 2 and 8 of "external administrating," adding the benzyl alcohol to the cultured cells in their dish would include externally administering the composition; in other words, the reference does disclose direct injection of the benzyl alcohol directly into the cells. The reference also indicated:

> Since we found out that Benzyl alcohol had antitumor effect to a stomach cancer, we report said effect herein.

which, absent factual evidence to the contrary would have been *in vivo* and since the gut space is "external" to the body, would have been anticipated as a method of external administration.

3) Claims 1-3, 5, 8, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by "The antitumor effect of benzyl alcohol against breast cancer," The 10th Annual Meeting of the Japanese Breast Cancer Society, July 5-6, 2002, B-323 (listed on PTO Form 1449, dated 27 October 2003, with a translation provided by Applicant), hereafter referred to as Reference B-323.

Reference B-323 benzyl alcohol induced cell death in breast cancer cells (in cell lines BSMZ and MCF-7). The reference also teaches that according to the apoptosis examination, Caspase-3 and 8 was "admitted in MCF-7" but not in the BSMZ cell line.

In reference to the limitation in instant claim 8 of "external administrating," adding the benzyl alcohol to the cultured cells in their dish would include externally administering the composition; in other words, the reference does disclose direct injection of the benzyl alcohol into the individual cells and the specification does not define "external administration".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4) Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smorenburg SM, et al., "The complex effects of heparin on cancer progression and metastasis in experimental studies," 2001 *Pharmacological Reviews* 53(1): p. 93-105, in view of Bessette (WO 00/33857), in light of *Stedman's Medical Dictionary*, 25th Edition (1990), p. 1026-1027 (cited for definition purposes).

Smorenberg et al. teaches heparins as anti-cancer drugs and that heparins affects survival rates of patients with cancer (abstract). In particular, the reference teaches treatment of subcutaneously implanted tumors of various types and their metastases, including mammary carcinoma, melanoma, and colon carcinoma (p. 95, Tables 1 and 2). Smorenberg also teaches that heparins affect progression of cancer in many ways: inhibiting intravascular arrest of cancer cells and thus their metastases due to their anticoagulation effect; binding growth factors and affecting proliferation and migration of cancer cells; inhibiting angiogenesis; and inhibiting oncogenes. (See p. 101, Conclusions). The secondary reference does not teach benzyl alcohol.

Bessette teaches a pharmaceutical composition for the treatment of soft tissue cancer in mammals comprising at least one plant essential oil compound and a specific embodiment where the plant oil is benzyl alcohol (see: abstract; reference claims 1, 2, 8, and 14) – see current

claims 1 and 3. The reference also teaches oral and parenteral administration (p. 6) as well as topical application to the skin (p. 7), which meets the limitation of current claim 2 and 8 as to external administration) of the composition to a patient in need thereof. The reference specifically teaches treatment of human breast cancer cells (MCF-7) with 50 μg/ml benzyl alcohol (see: p. 6; p. 11-12, Example 3) and thus, anticipates current claims 2, 8, and 9 as to breast and other cancers. The Bessette reference does not teach heparin or vitamin C.

Stedman's defines necrosis as "pathological death of one or more cells...resulting from irreversible damage" (p. 1026). Thus, absent any factual evidence to the contrary, the cell death occurring in the treatment methods of the prior art would be considered necrosis, according to the common medical definition by Stedman's, therefore meeting the limitation of "necrosis" as recited by instant claims 13-17.

In addition, the following case law is believed to be relevant to the instant claim rejections:

In re Kerkhoven (205 USPQ 1069, CCPA 1980) states that "It is *prima facia* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose: the idea of combining them flows logically from their having been individually taught in the prior art." Therefore, would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine heparin and benzyl alcohol, motivated by their having been taught by the prior art to be useful in treating cancerous tumors, consonant with the reasoning of the cited case law.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating stomach tumor cells (in cell lines STKM), breast tumor cells (in cell lines MCF7 and BSZM), large bowel tumor cells (in cell lines DLD and LOVO), thyroid gland tumor cells (in the cancer cell line SW1736), and pancreatic tumor cells (in the cell line PA-1) (see specification: pages 10-13 and 16-17, Examples 1-3 and 5) with benzyl alcohol, does not reasonably provide enablement for treating all types of cancer cells or all types of tumor growth *in vivo*. Also, the specification does not provide enablement for treating tumor cells for any other cancer types other than stomach, breast, large bowel, thyroid gland, and pancreatic tumor cells using benzyl alcohol. Additionally, the specification is not enabled for combination therapy of benzyl alcohol with heparin or vitamin C to treat tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Relative skill of those in the art.
4) Level of predictability in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1) The nature of the invention.

The claimed invention relates generally to chemotherapy, and specifically to compositions and methods for treating tumors without regard to the environment (see instant claim 1) which includes both *in vitro* and *in vivo*.

2) State of the prior art.

While the state of the art is relatively high with regard to the treatment of specific cancer types, the state of the art with regard to treating cancer broadly is underdeveloped. In particular, there is no known anticancer agent that is effective against all cancer cell types. The Cecil reference (*Textbook of Medicine, 21st Edition* (2000), Goldman & Bennett (Editors), W.B. Saunders Company (Publisher), Chapter 198, pages 1060-1074)

clearly shows that for the various known cancer types, there is no one specific chemotherapeutic agent that is effective for all types of cancer (see page Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

3) Relative skill of those in the art.

The relative skill of those in the art is high, generally that of a PHD/MD with several years of practical experience.

4) Level of predictability in the art.

The cancer treatment art involves a very high level of unpredictability as demonstrated by the state-of-the-art with regard to the treatment of specific cancers with specific agents and has long been underdeveloped with regard to the treatment of cancers broadly (see discussion in section *2)* above on the state of the prior art). The lack of significant guidance from the present specification or prior art with regard to the actual treatment of all types of cancer/tumor cells in a mammal, including a human subject, with the claimed active ingredients makes practicing the claimed invention unpredictable.

5) Amount of direction or guidance provided by the inventor & 6) Presence or absence of working examples.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating stomach tumor cells (in cell

lines STKM), breast tumor cells (in cell lines MCF7 and BSZM), large bowel tumor cells (in cell lines DLD and LOVO), thyroid gland tumor cells (in the cancer cell line SW1736), and pancreatic tumor cells (in the cell line PA-1) (see specification: pages 10-13 and 16-17, Examples 1-3 and 5)

The specification at pages 10-13, 16-17, and Examples 1-3 and 5 teach the specific treatment of stomach tumor cells (in cell lines STKM), breast tumor cells (in cell lines MCF7 and BSZM), large bowel tumor cells (in cell lines DLD and LOVO), thyroid gland tumor cells (in the cancer cell line SW1736), and pancreatic tumor cells (in the cell line PA-1) with benzyl alcohol. However, it does not teach combination treatment of benzyl alcohol with a second agent (heparin or vitamin C).

7) Breadth of claims.

The claims are very broad and inclusive of cancer cells and tumors generally. The breadth of the claims exacerbate the complex nature of the subject matter to which the present claims are directed. The claims are extremely broad due to the vast number of possible cancer types represented by the term "tumor."

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification does not enable any person skilled in the art to which it pertains (i.e. chemotherapy and treatment of cancer/tumors) to make or use the invention commensurate in scope with the claims. The lack of adequate guidance from the

specification or prior art with regard to the actual treatment of all cancers with benzyl alcohol or benzyl alcohol in combination with a second agent fails to rebut the presumption of unpredictability existent in this art. Applicants fail to provide the guidance and information required to ascertain which particular type of cancer the claimed anticancer agent will be effective against without resorting to undue experimentation. Applicant's limited disclosure with respect to benzyl alcohol alone to treat stomach, breast, large bowel, thyroid gland, and/or pancreatic tumor cells is noted but does not demonstrate treating all cancers.

Absent a reasonable *a priori* expectation of success for using a specific chemotherapeutic agent/combination to treat any particular type of cancer, one skilled in the art would have to extensively test many various tumor types. Since each prospective embodiment, and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

Pertinent Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure..

- Fukuda T, et al., "Anti-tumor promoting effect of glycosides from *Prunus persica* seeds," February 1, 2003 *Biol. Pharm. Bull.* 26(2): pages 271-273. The reference teaches anti-tumor activity of benzyl alcohol derivatives in carcinogenesis on mouse skin.

- Barett et al. (US Patents 6,492,363 and 6,310,060) teach benzyl alcohol derivatives for the treatment of various proliferative diseases, including various cancers.
- Ohmori et al. (US Patent 5,431,925) teaches a nutrient composition for patients being treated with anti-cancer agents containing vitamins and minerals, including vitamin C, as one of the major components (see abstract and claim 1).
- Jamison, JM, et al., "Autoschizis : a novel cell death," 2002 *Biochemical Pharmacology* 63: 1773-1783. The reference teaches that tumor cells are seen undergo necrosis, apoptosis and autoschizis all at once (p. 1775). The reference also defines autoschizis as a type of necrosis and that it may compliment apoptosis in antitumor activity (abstract & p. 1775).

Summary

Claims 1-17 are rejected. No claims are allowed.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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